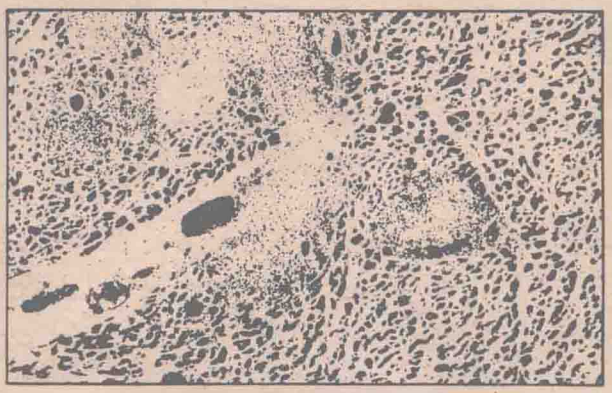
Immunology of Cardiovascular Disease



Edited by
Maurice H. Lessof

IMMUNOLOGY OF CARDIOVASCULAR DISEASE

Edited by Maurice H. Lessof

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Series Introduction

The current plethora of cardiovascular texts serves to question the need for yet another series of monographs on subjects cardiologic. The student of any age is faced with a series of choices so varied and plentiful that it is difficult to assess the strengths and significances of the current crop and, at the same time, remain unreasonably familiar with peer review publications in the field of one's own interest. Nevertheless, the series *Basic and Clinical Cardiology* of the publishing house of Marcel Dekker, Inc., has certain objectives that have persuaded the series editors that the endeavor has valued but different characteristics and, thus, has resulted in their participation. Of these, the first is perhaps underscored by the appointment of two series editors, one each from Europe and the United States; Henri Denolin of Brussels, Belgium, past President of the European Society of Cardiology; and Jeremy Swan of Los Angeles, California, past President of the American College of Cardiology. Since a commonality exists in the truths of the biological sciences and in the needs of patients with diseases of the heart and blood vessels, and in the social background requirements for community health, transatlantic cooperation and coauthorship should be fostered by this arrangement. Thus, it is hoped that the publications in this series will represent views from both sides of the North Atlantic Ocean and allow the sharing of knowledge of all colleagues without geographic restraint, but to mutual advantage.

The real justification for the production of a monograph or a series of monographs in an important discipline such as cardiovascular disease is to present, in a summarized form, a large body of relevant information which is reasonably current, critically assessed and succinctly presented. Thus, it is anticipated that the contributions in this series will range widely in their characteristics, but will effectively meet the appropriate requirements of the readers.

Professor Maurice H. Lessof of Guy's Hospital Medical School in London, England, has compiled an important text on the immunological aspects of cardiovascular disease. His authorship, although favoring contributions from Great Britain, includes authorities from the United States and South America. The result is a complete and authoritative text on a topic which is attaining ever-increasing importance in the field of both academic and practical cardiology. The chapter contributors present a scholarly, well-cited review of the different aspects of a field which is only recently attaining appreciation among practicing cardiologists. This comprehensive text will serve even the most critical reader, since it is a comprehensive source of current knowledge of the topic.

H. J. C. Swan, M.D., Ph.D.

Preface

The communications gap between scientific immunology and the clinician has always been wide, and to most practicing cardiologists the mysteries of immunology are profound. Yet the diseases which are encountered in a cardiologist's everyday practice have important immunological aspects, not only from the etiological point of view but also in diagnosis and management. For scientists, too, the immunological aspects of cardiovascular disease are highly relevant, especially for those who are concerned with animal models of disease or with transplantation and its sequelae, the immunology of connective tissue disorders, atherosclerosis or the post-cardiac-injury syndrome. The authors of this book have therefore attempted to provide information which will be useful for both physicians and scientists.

It is a pleasure to acknowledge the help of the distinguished contributors who have been willing to devote their time to this project. I am indebted to Mrs. Sally Kemsley for secretarial assistance. Last but not least, I am deeply grateful for the help (and the forbearance) of my wife Leila and our children, Nicholas, Susan and Caroline.

Maurice H. Lessof

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Contents

1 Immunological Mechanisms and Cardiovascular Disease

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I. INTRODUCTION

The object of this chapter is to review the principal mechanisms by which immunological processes damage tissues in cardiovascular diseases. Its conclusions are drawn almost exclusively from observations in man as opposed to animal experiments. It does not aim at describing the whole range of immune processes in detail since such reviews are already available both in general terms and in the context of clinical immunology.

There are two principal ways in which an analysis of immunological reactions might help to explain diseases of the cardiovascular system. First, ineffective immune reactions might allow microbial infections to become disseminated more extensively than in normal individuals or, by evading host immune mechanisms, to persist in abnormal sites. Pertinent examples relevant to cardiology are chronic myocarditis following virus infections or infection by *Trypanosoma cruzi* (Chagas' disease). Second, immunological reactions may damage the heart and blood vessels through a variety of mechanisms collectively termed allergic reactions. Thus, while the immune system is essential for protecting the host against a variety of infections, the immune response to foreign substances may precipitate disease. These two processes are often interrelated since the successful elimination of some microbial infections may inescapably be accompanied by immune reactions which produce the symptoms of disease. A simple example is the host response to infection by respiratory viruses. The immune response to these pathogens limits the extent and duration of infection but at the price of

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provoking the familiar features of the common cold. Conversely, the inability to eliminate an infectious agent through one or more forms of immunodeficiency can itself precipitate later immunopathological consequences. This point is illustrated by the immunopathological consequences of immune complex formation accompanying a persistent infection such as subacute bacterial endocarditis.

II. THE DEFINITION OF AN IMMUNOPATHOLOGICAL REACTION

We can define an immunological reaction simply as the specific combination of antigens with humoral antibody or sensitized cells. Immunopathological events are defined as tissue damage resulting from the initiation of immune reactions. However, it is not always easy to distinguish between damage inflicted by immune reactions and that resulting from other causes. Tissue damage, irrespective of its cause, commonly induces secondary changes with features characteristic of an immunological reaction. However detecting such reactions does not necessarily imply that the disease is primarily immunological in nature. An example is the spectrum of abnormalities produced by vinyl chloride poisoning. In addition to the acrosclerotic changes produced in the extremities, patients with severe disease induced by exposure to this material may develop hypergammaglobulinemia, autoantibodies, complement consumption, and a reduction in the numbers of circulating T lymphocytes (Ward et al., 1976). These changes are usually regarded as the hallmarks of an immunological disturbance, but there is no firm evidence that immune reactions contribute to the pathogenesis of this disorder. Similarly, acute anaphylaxis is a well-recognized clinical syndrome with such features as sweating, bronchoconstriction, and vasomotor collapse. However, while this disorder may result from specific immunological hypersensitivity to, for example, bee venom, it may also be provoked by hypersensitivity reactions which are not immunological in nature. It is necessary, therefore, to define precise criteria for attributing any disease process to an immunological mechanism (Table 1). Such an attribution can only be done convincingly when the precise antigens which invoke the immune response can be identified. This may prove to be an environmental antigen as, for example, grass pollen in allergic patients with seasonal allergic rhinitis, or an autoantigen in patients with, for example, autoimmune hemolytic anemia. In addition, the clinical situation must be carefully analyzed before any disease is considered to result from an immune mechanism, since immunological abnormalities may arise merely as the consequence of a given disorder. Such considerations are of practical as well as theoretical importance, since potent cytotoxic drugs are now widely used in some chronic inflammatory diseases for their allegedly immunosuppressive properties because these disorders are thought to result from abnormal immune reactions.

Table 1 Criteria for Attributing a Disease to Immune Mechanisms[a]

	Observation	Interpretation
1.	Identification of a potential immunogen (e.g., grass pollen in seasonal allergic rhinitis; or a drug in a "hypersensitivity" disorder) which provokes the disease	The relationship between exposure to the immunogen and provocation of the disease may be conclusive evidence for the cause but *not* necessarily for an immune mechanism; demonstration of "immunological memory" is convincing, i.e., re-exposure elicits a more rapid response
2.	Laboratory evidence for an immune reaction	
	a. Positive responses to challenge via the skin, respiratory tract or gut	Convincing if properly controlled and specific; some diseases may cause an exaggerated response to a variety of challenges.
	b. Detection of specific antibody	May be convincing (e.g., rise in specific IgE; autoantibodies with detectable pathological effects) but often hard to interpret (e.g., hypergammaglobulinemia produces nonspecific rise in antibody titer)
	c. Detection of immune response in tissues	Occasionally convincing (e.g., autoantibodies to glomerular basement membrane deposited in kidneys; more commonly uninterpretable (e.g., deposition of immunoglobulin and complement in various skin diseases such as pemphigus and pemphigoid)
	d. Serological abnormalities, i.e., circulating complexes, complement activation, antinuclear antibodies, lymphocytotoxins	Common findings which do *not* constitute conclusive proof that a disease is primarily mediated by immunological mechanisms
	e. HLA associations	Not yet proven to be markers for immune response (Ir) genes in most instances
3.	Response to treatment	
	a. Exclusion regimes	Can implicate a cause (e.g., gluten) but not necessarily an immune mechanism

Table 1 (Continued)

Observation	Interpretation
3. (Continued)	
b. Corticosteroids and cytotoxic drugs	Even a successful outcome rarely proves that these agents with multiple sites of action worked through specifically immunosuppressive effects

[a]This table gives a general outline of the criteria for diagnosing an immune disorder. Specific mechanisms are considered subsequently.

III. THE CLASSIFICATION OF IMMUNOLOGICAL DISORDERS

The classification of immune reactions by Gell and Coombs (see Gell et al., 1974) has proved a successful means of analyzing the basic patterns of immunological disorders. Type I is the so-called immediate hypersensitivity, involving reaginic antibody. Type II involves other cytotoxic effects of antibody. Type III depends on immune complexes and Type IV on delayed, cell-mediated immune reactions. However this classification has to be modified in two principal ways. First, immune disorders are rarely caused by a single mechanism in isolation but involve the interaction of several mechanisms. As will be discussed later, this is particularly true of the conventional distinction between "humoral" and "cell-mediated" immune reactions. Second, it is difficult to make a clear distinction between immunological and inflammatory events particularly in the context of chronic disorders. Many lesions initiated by immunologically specific events are perpetuated by inflammatory changes which are entirely nonspecific in nature. Nevertheless a broad classification facilitates the discussion of immune reaction in cardiovascular disorders and will be used as a framework for the following discussion (Table 2).

A. Disorders Mediated by Reaginic Antibody

Mechanisms of the Reaction

Reaginic antibody: Many allergic reactions are provoked by the combination of reaginic antibody with antigen which, in man, is usually identified as immunoglobulin E (IgE). IgE constitutes 1% at most of the total circulating serum immunoglobulin and its concentration does not normally exceed 0.003 mg/ml. Any increase in IgE concentration can be attributed to specific sensitization to one or more antigens. IgE attaches to basophils in the circulation and mast cells in the tissues (Fig. 1). On exposure to the provoking antigen, this antigen combines with IgE on the cell surface of these cells, thereby initiating

Table 2 Classification of Immune Reactions[a]

Diseases mediated by antibody

1. Reaginic antibody (IgE)
2. Other classes of antibody
   a. direct effects
   b. immune complex disease

Cell-mediated immunity

1. Specific immunity
   cytotoxic T lymphocytes
2. Nonspecific immunity
   a. Killer cells
   b. Natural killer cells
   c. Monocyte-macrophages

[a]This subdivision is largely artifical, as discussed in the text; most immunopathological diseases involve multiple reactions.

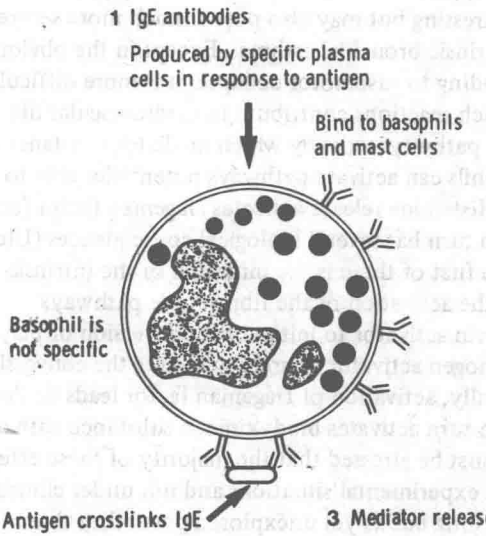

Figure 1 Mechanisms of mast cell and basophil sensitization by IgE.

degranulation and the release of mediator substances. Probably degranulation is a normal physiological process whereby basophils and mast cells secrete small amounts of material for prolonged periods, and this process is merely intensified when antigens attach to IgE on the cell surface (Padawer, 1979).

Mediators of immune response initiated by IgE: The mediator substances released by basophils and mast cells fall into two main categories.

The first category comprises substances that promote inflammatory reactions primarily by their action on smooth muscle and hence their ability to promote vasodilatation. The evidence incriminating histamine in allergic reactions is based upon both in vitro and in vivo assays for its release and on the therapeutic efficacy of antihistaminic drugs. However it has also to be recognized that histamine is efficiently removed from plasma following its intravenous administration and that most tissues have the capacity to degrade histamine rapidly (Beaven, 1976). The second mediator in this category is slow reacting substance of anaphylaxis (SRSA).

The second category of mediators released from basophils and mast cells are substances which are chemotactic for other cells, namely, platelets, granulocytes, and eosinophils. Whereas mediators released by granulocytes and platelets further contribute to the inflammatory reaction, eosinophils have the opposite effect by releasing enzymes which degrade histamine, SRSA, and the chemotactic factor specifically responsible for attracting platelets.

Cardiovascular consequences of immediate hypersensitivity reactions: It is well recognized that immediate hypersensitivity reactions not only provoke symptoms which are merely distressing but may also pose a much more severe problem in such disorders as extrinsic bronchial asthma. Except in the obvious context of acute anaphylaxis leading to vasomotor collapse, it is more difficult to decide the extent to which such reactions contribute to cardiovascular diseases. There is no question that pathways exist by which mediator substances released by mast cells and basophils can activate pathways potentially able to damage blood vessels (Fig. 2). Histamine release activates Hageman factor (coagulation factor XII), and this in turn has several biological consequences (Ulevitch and Cochrane, 1977). The first of these is the initiation of the intrinsic clotting system. The second is the activation of the fibrinolytic pathways through the ability of prekallikrein activator to initiate the conversion of plasminogen proactivator to plasminogen activator, thereby inducing the conversion of plasminogen to plasmin. Finally, activation of Hageman factor leads to the activation of kallikrein, which in turn activates bradykinin, a substance with a potent hypotensive action. It must be stressed that the majority of these effects have been observed in contrived experimental situations and not under clinical conditions. It remains an interesting but as yet unexplored possibility that chronic activation of these pathways might lead to irreversible vascular damage in human disease.